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Selective Synthesis of Enethiols

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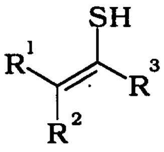
Abstract. Tautomerically pure aliphatic thioketones 3 have been prepared by treatment of dimethyl acetals with hydrogen sulfide in the presence of zinc chloride. Deprotonation with LDA leads to Z enethiolates 4 which were S-silylated with trimethylsilyl chloride to give silyl vinyl sulfides 5. Methanolysis of 5 quantitatively affords enethiols 1, devoid of the isomeric thioketones 3.

Enethiols **1** are tautomerically stable isomers of thioketones **3**. In contrast with the oxygen enol series, enethiols **1** have been isolated and characterised (1). However, they have only been prepared as mixtures with their isomeric thioketones (2). We wish to report the first selective preparation of aliphatic enethiols **1**.



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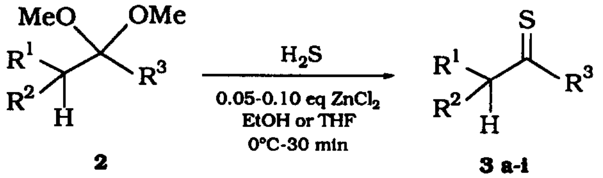
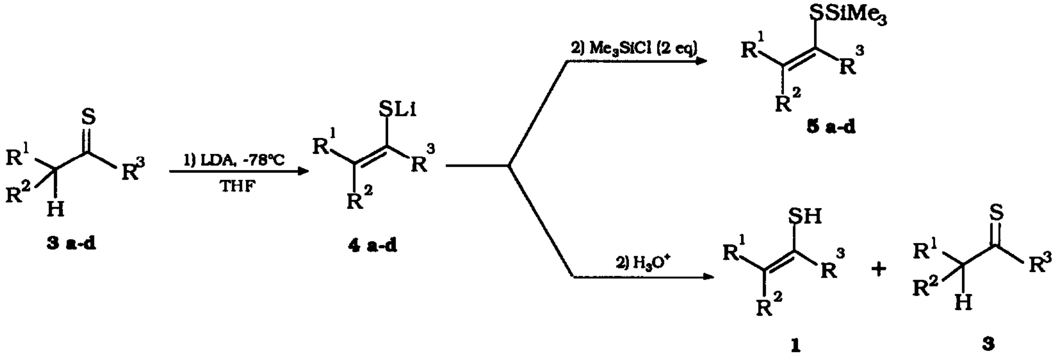
Our synthetic route involves S-protonation of silyl vinyl sulfides, accessible from thioketones. Methods for the preparation of thioketones from ketones have been reported (3, 4). They work reasonably well with non-enethiolizable cases. We checked them with aliphatic examples. Due to their fragility and easy isomerisation or oligomerisation, it is necessary to carry out this transformation under mild conditions. Inspired by an old method (5), we treated dimethylacetals **2** of ketones with hydrogen sulfide in ethanol or THF, at 0°C in the presence of 0.05-0.10 equivalents of zinc chloride. After work up and flash chromatography, red coloured thioketones **3** were isolated (6) in reasonable yields. It must be stressed that this method provides pure compounds **3**, devoid of enethiols **1**. To the best of our knowledge, this is the first selective preparation of enethiolisable thioketones **3**. It is very simple to carry out. These molecules can be kept in an inert atmosphere at -15°C without decomposition for one month.



a	$R^1 = R^2 = Me$, $R^3 = iPr$	Yield = 67 %
b	$R^1 = nC_4H_9$, $R^2 = H$, $R^3 = nC_5H_{11}$	54 %
c	$R^1 = nC_5H_{11}$, $R^2 = H$, $R^3 = nC_6H_{13}$	48 %
d	$R^1 = iPr$, $R^2 = H$, $R^3 = CH_2iPr$	60 %
e	$R^1 = R^2 = H$, $R^3 = tBu$	47 %
f	$R^1 = R^2 = H$, $R^3 = sBu$	36 %
g	$R^1 = Me$, $R^2 = H$, $R^3 = Pr$	42 %
h	$R^1 = Me$, $R^2 = H$, $R^3 =$ 2-Methylbutyl	45 %
i	$R^1 = nC_4H_9$, $R^2 = H$, $R^3 = iPr$	41 %

Compounds **3** were deprotonated by LDA under aprotic conditions (7). We restricted our study to the cases for which regio- and stereoselective deprotonation was observed. It is indeed achieved with symmetrical thiones **3a-d**. Furthermore, a single *Z* stereoisomer **4** was produced (8) from thiones **3b-d**, that we had already evidenced (7) for **4c**. It is remarkable that deprotonation of thiocarbonyl compounds always follows a ***cis*** process, whereas carbonyl derivatives, such as ketones and esters, lead (9) to ***trans*** enolates under the same conditions (LDA, THF)

We treated the expected enethiolates **4a-d** with various proton sources and found out that in all cases, mixtures of thioketones **3** and enethiols **1** were formed.

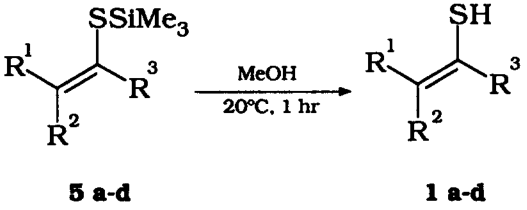


An alternative way might use the transformation of the enethiolate **4** and the creation of a weak sulfur-silicon bond that could be cleaved under mild non equilibrating conditions. Thus the enethiolates **4** were silylated selectively on the sulfur with trimethylsilyl chloride. Silyl vinyl sulfides **5a-d** were obtained quantitatively. Though rather simple, these molecules have not been reported so far from aliphatic thiones. We were surprised to observe that compounds **5** are reasonably stable, especially towards water traces, in contrast to silylketenedithioacetals (10, 11) which are very readily hydrolysed.

Cleavage of silyl vinyl sulfides **5** was easily accomplished by stirring with methanol at room temperature. After concentration the material was analysed by NMR. We were pleased to observe that enethiols **1** are formed selectively. No isomerisation to thioketones **3** takes place under these mild conditions. This methanolysis is kinetically controlled. It has been reported (12) that equilibrating conditions provide mixtures of **3** and **1** : for the example of **3a** the equilibrium ratio is 28 : 72. Even on standing for prolonged periods, our materials **1** remained unchanged.

Enethiols **1b-d** were obtained in the pure Z form as evidenced from their ^{13}C NMR spectra. We have already noted (7) the *cis* metallation of thioketones **3b-d** to give *cis* enethiolates **4**. Thus the following steps, silylation and methanolysis, occur with retention of configuration of the double bond.

This is the first report of a selective synthesis of enethiols, devoid of the isomeric thioketones. Analogous examples which are tautomers of thioaldehydes have been reported (13, 14) and appear thermodynamically stable. The observed stability of enethiols **1** is remarkable, especially when compared to the aliphatic enols which can be isolated only in biased systems or evidenced for a very short period of time or at low temperature.



This can be correlated to the poor 2s-3s orbital overlap between the carbon and sulfur of the C=S moiety of thioketones. Thus the thermodynamic stabilities of thioketones and enethiols are rather close (15).

Enethiols are now available for synthetic as well as mechanistic studies.

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6. **Synthesis of thioketones 3.**
   A solution of acetal **2** (30-70 mmol) and zinc chloride (0.05-0.1 equivalent) in ethanol (40 ml for 50 mmol) is cooled to 0°C. H_2S is bubbled through the solution over 30 min. After a few minutes a red colour appears. The extraction is executed by partition between pentane and a 0.1 N HCl solution. The organic solution is then washed with water, dried on $MgSO_4$ and concentrated. The crude material is purified by flash chromatography with pentane as eluent. Thioketones **3** are characterized by their NMR spectra (2).
   Synthesis of silyl vinyl sulfides 5.
   n-Butyllithium (0.6-1 mmol) is added dropwise to a THF solution of diisopropylamine (1 eq) cooled to -78°C. The solution is stirred for 15 min. The thioketone **3** (1 eq) is added dropwise. The red colour disappears. After stirring for 5-10 min, trimethylsilyl chloride (2 eq) is added in one portion. The mixture is stirred for 10 min at -78°C and then allowed to warm at room temperature. It is quenched with a saturated NH_4Cl aqueous solution and extracted with pentane. The organic layer is washed with water, dried on $MgSO_4$ and concentrated. Silyl vinyl sulfides **5** have been characterized by their ^1H and ^{13}C NMR spectra.
   Synthesis of enethiols 1.
   The silyl vinyl sulfide **5** (0.6-1 mmol) is stirred with methanol (4 ml) at room temperature for 1 hr. The mixture is concentrated. The crude material is pure enethiol **1** (NMR data: ref. 2).
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8. We have previously shown (7) that methylation of enethiolate **4c** leads to 7-methylthiotridec-6-ene to which Z structure was assigned by ^{13}C NMR according to ref (16). The carbon located β to SMe group was observed at 132.4 ppm (expected *Z* value: 131.2, *E* value: 123.9). We extended this Z assignment to the silyl derivatives **5b-d**: β carbons are found in a 127.5-130.0 range.
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